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09/977,864	10/15/2001	Henryk Dudek	CIBT-P01-104	3719
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

09/977,864

**Applicant(s)**

DUDEK ET AL.

**Examiner**

ZACHARY C. HOWARD

**Art Unit**

1646

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11 June 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1, 4-6, 8, 9, 21 and 23-67 is/are pending in the application.
- 4a) Of the above claim(s) 4, 6, 8 and 9 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 32-34 and 44-49 is/are allowed.
- 6) ☒ Claim(s) 1, 5, 21, 25, 26, 28, 30, 31, 35, 36, 38, 40-43, 50-53, 56, 57 and 60-67 is/are rejected.
- 7) ☒ Claim(s) 23, 24, 27, 29, 37, 39, 54, 55, 58 and 59 is/are objected to.
- 8) ☒ Claim(s) 1, 4-6, 8, 9, 21 and 23-67 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 April 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 6/11/08
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date: \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/11/08 has been entered.

### ***Status of Application, Amendments and/or Claims***

The amendment of 6/11/08 has been entered in full. Claims 4, 6, 8 and 60 are amended. Claim 7 is canceled. (Claims 2, 3, 10-20 and 22 were previously canceled). New claims 61-67 are added.

Claims 4, 6, 8 and 9 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim (see below). It is noted that Applicants listed claim 8 as "Currently amended"; however the correct status identifier for this claim is "Withdrawn - Currently amended". It is noted that claim 9 depends from claim 1 but recites a species of unwanted cell proliferation that is not encompassed by claim 1.

Claims 1, 5, 21 and 23-67 are under consideration in the instant application.

### ***Information Disclosure Statement***

The Information Disclosure Statement of 6/11/08 has been considered.

### ***Withdrawn Rejections***

The provisional rejection of claims 1, 5, 21 and 23-60 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of copending Application No. 10/652,298 is withdrawn in view of the amendments to claim 5 of the '298 Application (filed 6/11/08) that deletes the recitation of "colon cancer".

In view of the withdrawal of this rejection, claims 1, 5, 21 and 23-60 are allowable with respect to the elected species of "colon cancer". The species of cancer recited in claim 1 are currently presented as a Markush-type group. In accordance to Markush-type practice (MPEP 803.02), the examination will now be extended. In the instant case, the recitation of the species of "bladder" and "prostate" necessitates a provisional rejection of claims 1, 5, 21, 25, 26, 28, 30, 31, 35, 36, 38, 40-43, 50-53, 56, 57 and 64-66 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 68 of copending Application No. 10/652,298, and a provisional rejection of claims 61 and 64-67 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 70 of copending Application No. 10/652,298 (see below).

***Maintained Objections and/or Rejections***

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph, enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60 and 63-67 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for treating colon cancer, comprising determining whether colon cancer tissue overexpresses a *gli-1* or *Sonic hedgehog* gene and administering to a patient in need thereof an amount of a *hedgehog* antibody sufficient to decrease at least one of the growth or proliferation of the colon cancer tissue, wherein the colon cancer tissue overexpresses a *gli-1* gene or *Sonic hedgehog* gene, and wherein the *hedgehog* antibody binds to Sonic hedgehog protein and inhibits *hedgehog* signaling,

does not reasonably provide enablement for:

a method for treating colon cancer, comprising administering to a patient in need thereof an amount of a *hedgehog* antibody sufficient to decrease at least one of the growth or proliferation of the colon cancer tissue, wherein the colon cancer tissue

overexpresses a *gli-1* gene or *Sonic hedgehog* gene, and wherein the *hedgehog* antibody binds to Sonic hedgehog protein and inhibits *hedgehog* signaling.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection was set forth pg 3-5 of the 3/17/08 rejection for claim 60; new claims 63-67 are herewith added to the rejection.

Applicants' arguments (6/11/08; pg 11) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants submit that while they disagree with the rejection, claim 60 has been amended to include the recitation that the "colon cancer tissue overexpresses a *gli-1* gene". Applicants argue that the specification provides extensive guidance "regarding methods for treating various cancers that overexpress *gli-1* or *Sonic hedgehog*".

Applicants' arguments have been fully considered but are not found persuasive. Claim 60 previously differed significantly from the other pending claims by (1) not requiring determination of *gli-1* gene expression and (2) not requiring that the treated cancer tissue is cancer tissue that overexpresses *gli-1*. It is acknowledged that Applicants have amended claim 60 to include limitation #2. However, independent claim 60, as well as new independent claims 63 and 64 (and the corresponding dependent claims), still lack a step of determining the expression of the *gli-1* gene in the cancer tissue. This step is essential for the skilled artisan to practice the claimed method with any certainty of success. Without a determination of *gli-1* gene expression, the skilled artisan would merely have to guess (without any chance of certainty) as to whether or not a particular colon tumor has *gli-1* gene expression, and then determine if the method was successful if the tumor was inhibited.

As set forth previously, the art provides evidence that many colon tumors do not overexpress the *gli-1* or *Sonic hedgehog* genes. In U.S. Pre-Grant Application Publication 2004/0110663 (a publication of application 10/652,298, which is a continuation-in-part of the instant application), Applicants report that the growth of a xenograft of non-hedgehog expressing colon cancer cell line SW480 is not inhibited by

5E1 (Figure 54; ¶ 848 of the '663 publication). Furthermore, the relevant art teaches that "[c]ell lines might not be good models for the assessment of Hh pathway activity. However, the published results on primary human colon cancers are also confusing. Some authors, but not others detected increased levels of Hh pathway members during colon cancer progression. Moreover, the expression of Ihh and Gli1 were shown to be decreased during colon cancer progression in recent publications" (see pg 2626 of Chatel et al, 2007. Int J Cancer. 121: 2622-2627).

In order to practice the claimed method while excluding those tumors for which *gli-1* or *Sonic hedgehog* gene is not overexpressed, the skilled artisan must have a means of distinguishing such tumors. Thus, the claims require a step of determination of whether the *gli-1* or *Sonic hedgehog* gene is overexpressed in the tumor. The claims as originally filed were all directed to methods including step of determining *gli-1* gene expression. The specification as originally filed only describes methods including a determination step, and does not teach any methods where treatment is predictably applied without previously determining the status of the *gli-1* expression. Without such a step, the clinician will be practicing the claimed method "blindly", i.e., without any predictability as to the success of the method.

Due to the large quantity of experimentation necessary to determine how to successfully apply the claimed method to treat a colon tumor without measuring *gli-1* or *Sonic hedgehog* gene expression; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; and the unpredictability of distinguishing colon tumors amenable to anti-hedgehog antibody treatment without measuring *gli-1* or *Sonic hedgehog* gene expression, undue experimentation would still be required of the skilled artisan to make and/or use the claimed invention in its full scope.

#### ***New Rejections***

#### ***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 60 and 63-67 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are:

Claim 60 requires that "the colon cancer tissue overexpresses a *gli-1* gene", but omits the essential method step of determining that the colon cancer tissue overexpresses a *gli-1* gene (e.g., by measuring the expression of the *gli-1* gene). This method step is essential for the reasons set forth in the rejection under 35 U.S.C. 112, first paragraph (enablement).

Claim 63 requires that "the colon cancer tissue overexpresses a *Sonic hedgehog* gene", but omits the essential method step of determining that the colon cancer tissue overexpresses a *Sonic hedgehog* gene (e.g., by measuring the expression of the *Sonic hedgehog* gene). This method step is essential for the reasons set forth in the rejection under 35 U.S.C. 112, first paragraph (enablement).

Claim 64 requires that "the tumor overexpresses a *gli-1* gene or a *Sonic hedgehog* gene", but omits the essential method step of determining that the colon cancer tissue overexpresses a *gli-1* gene or a *Sonic hedgehog* gene (e.g., by measuring the expression of the *gli-1* or *Sonic hedgehog* genes). This method step is essential for the reasons set forth in the rejection under 35 U.S.C. 112, first paragraph (enablement).

The remaining claims are rejected for depending from an indefinite claim.

***Claim Rejections - 35 USC § 112, 1st paragraph, new matter***

Claims 61-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

Claim 61 is directed to a method for treating a tumor in a patient, comprising determining whether the tumor overexpresses a *Sonic hedgehog* gene and administering to said patient an amount of a *hedgehog* antibody sufficient to decrease at least one of the growth or proliferation of the tumor, which *hedgehog* antibody binds

to the Sonic hedgehog protein and inhibits hedgehog signaling, wherein the tumor overexpresses a Sonic hedgehog gene and wherein the tumor is associated with at least one of urogenital, breast, prostate, bladder, or colon cancer. Applicants' remarks (6/11/08; pg 10) indicate that support for the new claims can be found in paragraphs 23, 55, 61, 62, 66 and 715-717 of the published application. These paragraphs, and the entirety of the originally filed specification, have been reviewed but do not provide support for new claim 61. Paragraph 23 describes contacting cells that overexpress a *gli* gene with an effective amount of a hedgehog antagonist, but contains nothing regarding hedgehog gene overexpression. Paragraph 66 is the first paragraph of an overview of the invention, but again nothing is stated regarding hedgehog gene overexpression. Paragraphs 55, 61 and 62 constitute the Brief Description of Figures 28, 34 and 33, which describe specific results shown in the respective figures. Paragraphs 715-717 relate to "Hedgehog Signaling in Bladder Cancer". This does include the statement that "shh expression is increased 12-fold ... in a bladder tumor sample when compared to normal adult bladder". However, there is no teaching in the specification relating these results to a treatment method as claimed. What is missing from the specification are specific teaching indicating that a method of treatment of a tumor that includes (1) determining whether the tumor overexpresses a *Sonic hedgehog* gene (as opposed to a *gli-1* gene) and (2) administering an antibody to a tumor that overexpresses a *Sonic hedgehog* gene (as required by the recitation of "wherein the tumor overexpresses a *Sonic hedgehog* gene"). The specification only teaches such treatment methods as they related to overexpression of the *gli-1* gene. Therefore, claim 61 contains new matter.

Claim 62 depends from claim 61 and limits the tumor to a colon tumor. Claim 62 contains new matter for the same reason as claim 61.

Claim 63 is directed to a method for treating colon cancer, comprising administering to a patient in need thereof an amount of a hedgehog antibody sufficient to decrease at least one of the growth or proliferation of the colon cancer tissue, wherein the hedgehog antibody binds to Sonic hedgehog protein and inhibits hedgehog signaling, and wherein the colon cancer tissue overexpresses a *Sonic hedgehog* gene. As described above, what is missing from the specification is a specific teaching



indicating that a method of treatment that includes administering an antibody to patient having colon cancer that overexpresses a *Sonic hedgehog* gene (as required by the recitation of "wherein the colon cancer overexpresses a *Sonic hedgehog* gene").

Claims 64 contains new matter for the same reason as claim 63; i.e., the claim recites "wherein the tumor overexpresses a ... a *Sonic hedgehog* gene..." Claims 65-67 depend from claim 64 and each encompass the same new matter as claim 64.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 21, 25, 26, 28, 30, 31, 35, 36, 38, 40-43, 50-53, 56, 57 and 64-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 68 of copending Application No. 10/652,298. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Each of instant claims 1, 5, 26 and 64-66 fully encompasses the method of claim 68 of the '298 application, in so far as it is drawn to the species of cancer of the "prostate" or "bladder" tissues. Claim 68 of the '298 application encompasses a method comprising determining whether diseased tissue overexpresses a *gli-1* gene, and contacting an overexpressing tissue with an anti-Sonic hedgehog antibody that inhibits *hedgehog* signaling in order to treat the cancer, wherein the tissue is associated with

prostate or bladder cancer. Therefore, claim 68 of the '298 anticipates each of instant claims 1, 5 and 64-66.

Claims 21, 25, 28, 30 and 31 are of similar scope to instant claim 1, but limit the method to one performed in a patient (i.e., *in vivo*). The specification of the '298 application indicates that *in vivo* treatment is a preferred embodiment of the claimed methods; therefore, claim 68 also anticipates instant claims 21, 25, 28 and 30.

Claims 35, 36 and 38 depend from one of the above claims and limit the parent claim to one wherein the gene measurement is made in a sample obtained from a tumor in a patient. This further limitation is also a preferred embodiment of the '298 application, as evidenced by claim 72 (presented 12/26/07 in the '298 application). Therefore, claim 68 of the '298 application also anticipates claims 35, 36 and 38.

Claims 40-43, 50-53, 56 and 57 each depend from one of the above claims and limit the parent claim to one wherein the *gli-1* overexpression is determined by measuring protein or transcript. These further limitations are also preferred embodiments of the '298 application, as evidenced by claims 76 and 77 (presented 12/26/07). Therefore, claim 68 of the '298 application also anticipates claims 40-43, 50-53, 56 and 57.

Claims 61 and 64-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 70 of copending Application No. 10/652,298. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Each of instant claims 61 and 64-67 fully encompasses the method of claim 70 of the '298 application. Claim 70 of the '298 application encompasses a method comprising determining whether diseased tissue overexpresses a *Sonic hedgehog* gene, and contacting an overexpressing tissue with an anti-Sonic hedgehog antibody that inhibits *hedgehog* signaling in order to treat the cancer, wherein the tissue is associated with prostate or bladder cancer. Therefore, claim 68 of the '298 anticipates each of instant claims 61 and 64-67.

In the 6/11/08 response (pg 15), Applicants "contend that the claims, as amended, in the instant and co-pending applications are patentable in view of each other. Nevertheless, Applicants ask that this rejection be held in abeyance until indication of allowable subject matter. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter".

The Examiner notes Applicants' intention of submitting a terminal disclaimer; however, the rejection is maintained. See MPEP 804.I.B: "The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications."

### ***Conclusion***

Claims 23, 24, 27, 29, 37, 39, 54, 55, 58 and 59 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 32-34 and 44-49 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./  
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/  
Primary Examiner, Art Unit 1646